



TITLE:

Gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide signaling in adipose tissue

AUTHOR(S):

Yamane, Shunsuke; Harada, Norio

CITATION:

Yamane, Shunsuke ...[et al]. Gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide signaling in adipose tissue. Journal of Diabetes Investigation 2019, 10(1): 3-5

ISSUE DATE:

2019-01

URL:

<http://hdl.handle.net/2433/241649>

RIGHT:

© 2018 The Authors. Journal of Diabetes Investigation published by Asian Association for the Study of Diabetes (AASD) and John Wiley & Sons Australia, Ltd.; This is an open access article under the terms of the Creative Commons Attribution - NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide signaling in adipose tissue

INTRODUCTION

Obesity has been recognized as a worldwide problem, especially for developing insulin resistance and increasing the risk of type 2 diabetes. The increased adipose tissue associated with obesity secretes various kinds of cytokines, adipokines and lipokines, and triggers systemic inflammatory response, resulting in the disturbance of metabolic homeostasis.

Gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide (GIP) is an incretin secreted from enteroendocrine K cells in response to meal ingestion¹, and potentiates insulin secretion through the GIP receptor (GIPR) expressed in pancreatic β -cells². Dietary lipid is a very strong stimulant of GIP secretion. For example, the peak value of GIP increase in response to a high-fat meal (450 kcal containing 33.3% of fat) is threefold higher than that in the 75-g oral glucose tolerance test in human subjects, suggesting that fat content in a mixed meal strongly stimulates GIP secretion¹. Chronic high-fat consumption induces hypersecretion of GIP from K cells³, and insulin secretion in response to GIP is enhanced in high-fat diet (HFD)-fed obese mice compared with that in lean mice fed a normal-fat diet⁴, indicating that GIPR signaling plays a critical role in postprandial hyperinsulinemia associated with chronic HFD feeding and the subsequent increase in lipoprotein lipase activity, which results in HFD-induced fat accumulation (Figure 1). Actually, reduction in GIPR signaling using systemic GIPR knockout (GIPR^{-/-}) mice⁵, a GIP antagonist⁶ and GIP immunoneutralization ameliorates obesity under HFD-fed conditions. In addition, we have reported that genetic deletion of GIP alleviates obesity and lessens the degree of insulin resistance in HFD-fed mice⁷. In contrast, given that functional GIPR is expressed in rodent and human adipocytes, it has been assumed that GIP also has direct effects on adipose tissue and plays some roles in lipid metabolism under HFD-fed conditions.

GIP SIGNALING IN ADIPOSE TISSUE

In vitro studies have shown that GIP directly induces fat accumulation in adipose tissue by increasing lipoprotein lipase expression through the cyclic adenosine monophosphate response element-binding protein (CREB)-regulated

transcription coactivator 2-mediated pathway, and by increasing lipoprotein lipase enzyme activity and plasma membrane glucose transporter 4 expression through the protein kinase B (PKB)-mediated pathway⁸. However, the physiological significance of GIPR signaling in adipocytes, namely, whether GIPR expressed in adipose tissue plays some roles in HFD-induced obesity and insulin resistance *in vivo*, has remained unproven.

To address this problem, we generated adipose tissue-specific GIPR knockout (GIPR^{adipo-/-}) mice⁹. Under HFD-fed conditions, GIPR^{adipo-/-} mice had significantly lower bodyweight and lean body mass compared with those in floxed GIPR (GIPR^{fl/fl}) mice, although the fat volume was not significantly different between the two groups. Interestingly, insulin resistance, liver weight and hepatic steatosis were reduced in HFD-fed GIPR^{adipo-/-} mice compared with those in GIPR^{fl/fl} mice. Microarray analysis of adipose tissues showed that expression of interleukin-6 (IL-6), a pro-inflammatory cytokine that induces insulin resistance and hepatic steatosis¹⁰, was significantly decreased in adipose tissue of GIPR^{adipo-/-} mice, and plasma levels of IL-6 were also reduced in HFD-fed GIPR^{adipo-/-} mice compared with those in HFD-fed GIPR^{fl/fl} mice.

Previous *in vitro* studies have shown that GIP increases IL-6 expression levels in adipose tissue¹¹. In astrocytes, CREB activated by β -adrenergic receptor enhances IL-6 expression induced by tumor necrosis factor (TNF)- α receptor signaling¹². It has been reported that GIP activates CREB in adipose tissue¹³. In our study using differentiated 3T3-L1 adipocytes, IL-6 expression was significantly augmented by GIP in the presence of TNF- α , suggesting that GIP enhances IL-6 messenger ribonucleic acid (mRNA) expression induced by TNF- α in adipose tissue, possibly through CREB activation.

Suppressor of cytokine signaling (SOCS) protein is induced by the activation of cytokine receptors, including the IL-6 receptor, TNF- α receptor and Toll-like receptors, and attenuates cytokine signal transduction¹⁴. Seven SOCS proteins have been identified, and SOCS1 and SOCS3 were recently reported to negatively regulate insulin signaling by competitively interfering with insulin receptor substrate binding to the insulin receptor¹⁵, by inhibiting insulin receptor autophosphorylation¹⁶ and by

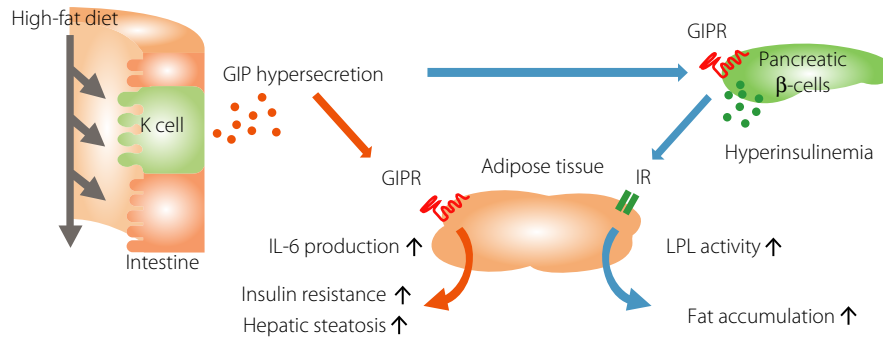


Figure 1 | Schematic representation illustrating potential mechanisms by which GIP hypersecretion in high-fat diet conditions induces insulin resistance and hepatic steatosis. GIP, gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide; GIPR, gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide receptor; IR, insulin receptor; IL-6, interleukin-6; LPL, lipoprotein lipase.

promoting proteasomal degradation of insulin receptor substrate¹⁷. In particular, SOCS3 signaling is located downstream of the IL-6 receptor¹⁴, and is associated with insulin resistance and hepatic steatosis¹⁸. Our *in vitro* experiments showed that GIP induced mRNA expression of IL-6 and SOCS3 in the presence of TNF- α in differentiated 3T3-L1 adipocytes. In addition, expression levels of SOCS3 mRNA were decreased in adipose and liver tissues of GIPR^{adipo-/-} mice. These results suggest that a decrease in SOCS3 expression by GIPR deficiency might enhance insulin sensitivity and potentiate PKB phosphorylation in adipose and liver tissues. However, SOCS3 mRNA expression in skeletal muscle was not different between the two groups of mice, although PKB phosphorylation was increased in the skeletal muscle of GIPR^{adipo-/-} mice. Further study is required to clarify the mechanism of the increase in insulin-induced PKB phosphorylation in the skeletal muscle of GIPR^{adipo-/-} mice.

It has also been reported that SOCS3 binds to the gene promoter of sterol regulatory element-binding protein-1c (SREBP-1c), which has critical roles in fat synthesis in the liver, and increases SREBP-1c mRNA expression¹⁸. Suppression of SOCS3 expression in *db/db* mice improves the hepatic steatosis through downregulation of SREBP-1c¹⁹. In our study, SREBP-1c and SOCS3 mRNA expression were decreased in the liver of HFD-fed GIPR^{adipo-/-} mice, indicating that deletion of GIPR signaling in adipocytes results in the decrease in IL-6 production from adipose tissue and subsequent fat synthesis in the liver through the IL-6–SOCS3–SREBP-1c pathway.

Although GIPR function in human adipose tissue is still unclear *in vivo*, *in vitro* study shows that GIP induces IL-6 mRNA expression and potentiates IL-6 secretion in the presence of TNF- α in human adipocytes¹¹, which is consistent with our data showing that IL-6 mRNA expression is decreased in the adipocytes of HFD-fed GIPR^{adipo-/-} mice.

Based on the phenotypes of GIPR^{adipo-/-} mice, it can be concluded that GIPR signaling in adipose tissue plays an important

role in HFD-induced insulin resistance and hepatic steatosis *in vivo*, with no direct effect on fat accumulation, through IL-6 signaling (Figure 1).

FUTURE PERSPECTIVE


As shown above, there is sufficient evidence to confirm that GIP is an obesity-promoting factor in HFD conditions and that deletion of GIPR signaling causes resistance to diet-induced obesity. Additionally, we have reported that partial reduction of GIP alleviates obesity and lessens the degree of insulin resistance under HFD conditions⁷. These findings suggest that regulation of GIPR signaling, especially after fat intake, is a promising therapeutic approach to obesity and type 2 diabetes. GIP antagonism is one of the candidates for GIP-based treatment for diabetes and obesity. However, the results in mice are not necessarily recapitulated in humans. For example, previously developed (Pro3) GIP as a potent antagonist of GIPR in mice was shown to stimulate GIPR in humans²⁰. In addition, given that GIPR is also expressed in various tissues, except for pancreatic β -cells and adipocytes, including the gastrointestinal tract, heart, inner layers of the adrenal cortex and several brain regions, further investigation is required to establish the systemic biological action of GIP before the implementation of GIPR antagonism as an anti-obesity/diabetes therapy to minimize unexpected adverse events.

ACKNOWLEDGMENTS

This study was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology (MEXT); Japan Society for the Promotion of Science; Ministry of Health, Labor and Welfare; Ministry of Agriculture, Forestry and Fisheries; Japan Diabetes Foundation; Japan Association for Diabetes Education and Care; Merck Sharp & Dohme (MSD); Novo Nordisk Pharma; and Banyu Life Science Foundation International.

DISCLOSURE

The authors declare no conflict of interest.

Shunsuke Yamane, Norio Harada* 

Department of Diabetes, Endocrinology and Nutrition,
Graduate School of Medicine, Kyoto University, Kyoto, Japan

*E-mail: nharada@kuhp.kyoto-u.ac.jp

REFERENCES

1. Yamane S, Harada N, Hamasaki A, *et al.* Effects of glucose and meal ingestion on incretin secretion in Japanese subjects with normal glucose tolerance. *J Diabetes Investig* 2012; 3: 80–85.
2. Seino Y, Yabe D. Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1: incretin actions beyond the pancreas. *J Diabetes Investig* 2013; 4: 108–130.
3. Suzuki K, Harada N, Yamane S, *et al.* Transcriptional regulatory factor X6 (Rfx6) increases gastric inhibitory polypeptide (GIP) expression in enteroendocrine K-cells and is involved in GIP hypersecretion in high-fat diet-induced obesity. *J Biol Chem* 2013; 288: 1929–1938.
4. Harada N, Yamada Y, Tsukiyama K, *et al.* A novel GIP receptor splice variant influences GIP sensitivity of pancreatic beta-cells in obese mice. *Am J Physiol Endocrinol Metab* 2008; 294: E61–E68.
5. Miyawaki K, Yamada Y, Ban N, *et al.* Inhibition of gastric inhibitory polypeptide signaling prevents obesity. *Nat Med* 2002; 8: 738–742.
6. McClean PL, Irwin N, Cassidy RS, *et al.* GIP receptor antagonism reverses obesity, insulin resistance, and associated metabolic disturbances induced in mice by prolonged consumption of high-fat diet. *Am J Physiol Endocrinol Metab* 2007; 293: E1746–E1755.
7. Nasteska D, Harada N, Suzuki K, *et al.* Chronic reduction of GIP secretion alleviates obesity and insulin resistance under high-fat diet conditions. *Diabetes* 2014; 63: 2332–2343.
8. Kim SJ, Nian C, McIntosh CH. GIP increases human adipocyte LPL expression through CREB and TORC2-mediated trans-activation of the LPL gene. *J Lipid Res* 2010; 51: 3145–3157.
9. Joo E, Harada N, Yamane S, *et al.* Inhibition of gastric inhibitory polypeptide receptor signaling in adipose tissue reduces insulin resistance and hepatic steatosis in high-fat diet-fed mice. *Diabetes* 2017; 66: 868–879.
10. Sabio G, Das M, Mora A, *et al.* A stress signaling pathway in adipose tissue regulates hepatic insulin resistance. *Science* 2008; 322: 1539–1543.
11. Chen S, Okahara F, Osaki N, *et al.* Increased GIP signaling induces adipose inflammation via a HIF-1 α -dependent pathway and impairs insulin sensitivity in mice. *Am J Physiol Endocrinol Metab* 2015; 308: E414–E425.
12. Spooren A, Kooijman R, Lintermans B, *et al.* Cooperation of NF κ B and CREB to induce synergistic IL-6 expression in astrocytes. *Cell Signal* 2010; 22: 871–881.
13. Mohammad S, Ramos LS, Buck J, *et al.* Gastric inhibitory peptide controls adipose insulin sensitivity via activation of cAMP response element-binding protein and p110 β isoform of phosphatidylinositol 3-kinase. *J Biol Chem* 2011; 286: 43062–43070.
14. Johnston JA, O'Shea JJ. Matching SOCS with function. *Nat Immunol* 2003; 4: 507–509.
15. Galic S, Sachithanandan N, Kay TW, *et al.* Suppressor of cytokine signalling (SOCS) proteins as guardians of inflammatory responses critical for regulating insulin sensitivity. *Biochem J* 2014; 461: 177–188.
16. Trengove MC, Ward AC. SOCS proteins in development and disease. *Am J Clin Exp Immunol* 2013; 2: 1–29.
17. Ueki K, Kondo T, Kahn CR. Suppressor of cytokine signaling 1 (SOCS-1) and SOCS-3 cause insulin resistance through inhibition of tyrosine phosphorylation of insulin receptor substrate proteins by discrete mechanisms. *Mol Cell Biol* 2004; 24: 5434–5446.
18. Xu X, So JS, Park JG, *et al.* Transcriptional control of hepatic lipid metabolism by SREBP and ChREBP. *Semin Liver Dis* 2013; 33: 301–311.
19. Ueki K, Kondo T, Tseng Y-H, *et al.* Central role of suppressors of cytokine signaling proteins in hepatic steatosis, insulin resistance, and the metabolic syndrome in the mouse. *Proc Natl Acad Sci USA* 2004; 101: 10422–10427.
20. Sparre-Ulrich AH, Hansen LS, Svendsen B, *et al.* Species-specific action of (Pro3)GIP - A full agonist at human GIP receptors, but a partial agonist and competitive antagonist at rat and mouse GIP receptors. *Br J Pharmacol* 2016; 173: 27–38.

Doi: 10.1111/jdi.12942